

## REMARKS

Reconsideration of the present application, as amended, is respectfully requested.

The present application contains pending claims 4-6, 8, 11, 17-20, 25, 46, 57-59, and 68-73 and new claims 74-79. The specification supports new claims 74-79 (see page 10 of the specification); as such, no new matter has been introduced with the addition of these claims. Claims 1-3, 7, 9, 10, 12-16, 21-24, 26-45, 47-56 and 60-67 have been canceled. Claims 25, 57, 58, 59, 68 have been amended.

### Rejections Under Section 112

Pending claims 4-6, 8, 11, 17-20, 25, 46, 57-59, and 68-73 stand rejected under 35 U.S.C. § 112, second paragraph. Claim 68 has been amended to clarify the interrelationship among the analyte, acceptor species and surface of the solid phase. In addition, claim 68, step b) has been amended to provide a proper antecedent basis for “bound acceptor species.”

The examiner has also asserted that claim 68 is indefinite because it lacks a correlation step with respect to detecting or quantifying an analyte. The Applicant respectfully traverses, because it is submitted that one of ordinary skill in the art, after reading the claims and specification, would understand how an analyte in a sample is differentially detected if present or otherwise. For example, it would be appreciated that the possible formats of the assay may occur in various manners allowing for detection. These manners of detection are provided in the specification of the present application, are known to those in the art and are even specifically enumerated in dependent claims. As a non-limiting example, in claim 69, detection is determined “by quenching of emission of said energy donor species or by sensitized emission of said energy acceptor

species.” Another non-limiting example is provided in claim 70 where detection is determined “by a change in luminescence decay rate of said energy donor species.” That detection occurs with certain limitations is clear from the claim language; further limitation would unduly limit the breadth of the claim. Applicant believes that the examiner’s assertion impermissibly mistakes a breadth of scope for indefiniteness and that a proper *prima facie* case of indefiniteness has not been made. .

With respect to examiner’s rejection of claims 46 and 71-73 for the “same analogous problems,” claims 46 and 71-73 are believed to be allowable for the reasons presented above for claim 68..

In view of the foregoing, it is respectfully requested that the rejection of claims 68, 46, and 71-73 under 35 U.S.C. §112, second paragraph, be withdrawn.

Claims 25, 58, and 59 have been amended to delete the recitation of “and other proteins.”

Applicant respectfully submits that claims 4-6, 8, 11, 17-20, 25, 46, 57-59, and 68-73, as amended, comply with 35 U.S.C. § 112 and that the rejection thereof be withdrawn.

### **Rejection Under Section 103**

Pending claims 4-6, 11, 17-20, 25, 57, 58, and 68-73 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Zarling et al. (U.S. Patent 5,736,410) in view of Selvin et al. (U.S. 5,622,821). Applicant respectfully traverses this rejection for the following reasons.

The examiner’s analysis of Zarling in Section 6 of the Official Action (beginning on page 5 and running to the first paragraph on page 7) is generally accurate, but does not

address certain aspects of the present invention. In particular, the examiner's assertion that Zarling differs from the present invention in "failing to teach a luminescence assay based on detection of energy transfer between an energy donor species and an energy acceptor species wherein the analyte causes a change in the proximity between the donor species and the acceptor species" is accurate, but does not properly frame the non-obviousness found in the present invention.

Zarling does not suggest that the up-converted emission can be transferred to an acceptor for the purposes of an assay, a non-obvious distinction between Zarling and the present invention. Zarling teaches use of up-converting labels in various assay formats, such as those described on the paragraph bridging columns 20 and 21 of Zarling. Of note, Zarling is using the up-conversion particle purely as a label. In other words, the particle is excited with electromagnetic radiation of the appropriate wavelength and up-converted emission is detected. Zarling does not suggest that the up-converted emission can be transferred to an acceptor for the purposes of an assay (as is the case of the present invention). While not the only unobvious distinction, this distinction is more important than the examiner's brevity in addressing it would seem to indicate. This is particularly so because Zarling does contemplate emission from the up-converted medium for producing targeted damage (e.g. catalysis) in chemical or biological materials. (*see* first paragraph, column 7; and the description beginning at column 7, line 27 of Zarling. In particular, the applicant references the examiner to the description at column 28, lines 10-23 which refers to the up-converting medium (i.e. a donor) transferring energy to a dye (an acceptor) which subsequently transfers its energy to a dissolved molecular oxygen molecule.) It is clear, therefore, that Zarling had not contemplated use of his up-

converting particles in an energy transfer. Zarling did contemplate transfer of electromagnetic radiation to an acceptor (see above), but only in the context of producing targeted damage.

Selvin does relate to an energy transfer assay and the examiner's summary is broadly correct; however, as with Zarling, the examiner's analysis does not address certain aspects of the present invention. As a non-limiting example, Selvin discloses lanthanide chelates with the chelating molecule being a polynuclear heterocyclic aromatic sensitizer of the general formula shown at the top of column 2 of Selvin. The chelate molecules are useful in resonance energy transfer assays, e.g. as broadly disclosed at column 2, line 51-54. Although Selvin discloses lanthanides as a class, the specific examples given are terbium and europium (column 2, lines 31-32).

The examiner has combined Zarling and Selvin, stating: "... Selvin specifically taught that lanthanide ions which are used by Zarling as up-converting phosphor labels are amenable to luminescence resonance energy transfer methods for assaying the presence or amount of analyte in a sample." (final paragraph on page 7 of the Official Action).

Respectfully, the Examiner has not provided a sufficient basis to combine Zarling and Selvin as a basis for rejection under 35 U.S.C. § 103. The seminal case directed to application of obviousness is Graham v. John Deere, 383 U.S. 1; 148 USPQ 459 (1966). From this case, four familiar factual inquiries have resulted. The first three are directed to the evaluation of prior art relative to the claims at issue, and the last is directed to evaluating evidence of secondary considerations. See, MPEP §2141.

From these inquiries, the initial burden is on the Examiner to establish a *prima facie* case of obviousness for which three basic criteria must be met. "First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure." MPEP §2142 (*citing, In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)). The suggestion/motivation to combine or modify under §103 needs to be specific. Where a "statement is of a type that gives only general guidance and is not specific as to the particular form of the claimed invention and how to achieve it ... [s]uch a suggestion may make an approach 'obvious to try' but it does not make the invention obvious." *Ex parte Obukowicz*, 27 USPQ2d 1063, 1065 (U.S. Pat. and Trademark Off. Bd. of Pat. App. & Interferences 1993) (citations omitted). "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." MPEP §2141.02 (*citing, W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540; 220 USPQ 303 (Fed. Cir. 1983)).

Selvin discloses an assay based on a complex of a lanthanide (specifically terbium and europium) with a particular type of chelating ligand. The skilled person might find it obvious to modify the Selvin assay by using a modification of the ligand specifically disclosed by *Selvin*. However, the skilled person would not take the step of a "wholesale" replacement of Selvin's chelated lanthanide by an up-conversion phosphor

of the type disclosed by Zarling. This is particularly so because Selvin does not consider the use of a particulate energy donors or surfaces (as found in the present invention) in any embodiment. Therefore, modification of Selvin by Zarling to arrive at the present invention requires not only a change for a chelated lanthanide (specifically terbium and europium) but also a significant change in the format of the Selvin assay.

There is still less incentive to modify Selvin by Zarling when one considers (as discussed above) that, for the purposes of any assay, Zarling only contemplates use of his up-converting label as just that – a label – without any suggestion of energy transfer. If Selvin is to be modified by Zarling then (in addition to the points made above) surely the skilled person must be given at least a hint in Zarling of employing energy transfer from the up-converting label for the purposes of an assay. No such motivation or suggestion is given since, for the purposes of an assay, Zarling uses his labels in what might be called a “passive” sense because the presence of the label (to determine the outcome of an assay) is detected purely on the basis of the emission from the up-conversion label. The reference in Zarling to producing targeted damage in chemical or biological materials (Zarling, column 7) does not provide that suggestion, or even a suggestion that would approach this modification. In a similar vein, Selvin does not consider the possibility of using his chelated lanthanides (specifically terbium and europium) as up-converting energy donors, but rather describes how lanthanides that are highly luminescent are useful on the basis of their long luminescence decay times, which are typically greater than 100 microseconds. Once again, therefore, there is no suggestion or motivation to modify Zarling in light of Selvin.

It would further not have been obvious to modify Zarling in light of Selvin because Selvin has certain drawbacks that, if combined with Zarling, would not result in the understanding that is provided in the present invention. The lanthanides that are most useful for the present invention are able to upconvert light efficiently, but are very weakly luminescent or non-luminescent in complexes, such as those described by Selvin et al. The reason for this distinction is that the low-lying excited states that are essential for up-conversion to be efficient provide opportunities for the upper states responsible for luminescence to be depopulated by vibrational coupling to phonons in the medium. Consequently luminescence is severely quenched and luminescence decay times are very short except when the up-converting lanthanide is protected in a host lattice that has a low phonon energy. By contrast, the organic complexes described by Selvin et al. are highly efficient when excited conventionally but are very inefficient in up-conversion because they lack suitable intermediate states. This protects them from vibrational deactivation and allows the upper states to have long emissive lifetimes.

The assay described by Selvin et al. is limited to a resonance energy transfer process that has a very short effective distance, of the order of a few nanometres at most. In contrast the present invention has no limitation to resonance processes and assays based, for example, on reabsorption of emitted up-converted radiation are possible. Reabsorption of emitted light does not change the luminescence decay time of the emissive species so this measurement would not be appropriate to detect such reabsorption and emission intensity measurements or measurements of luminescence of the energy acceptor would be substituted in such a case. Reabsorption-based assays are

advantageous in principle because they have much less steep distance dependence than resonance processes as described by Selvin et al.

Selvin et al. do not consider the use of particulate energy donors or surfaces in any of their embodiments to our knowledge. In the present invention this is one of the non-obvious features which provides protection from vibrational deactivation, thereby facilitating up-conversion.

For at least the foregoing reasons, claim 68, as amended, is believed to be allowable. Dependent claims 4-6, 8, 11, 17-20, 25, 46, 57-59 are also believed to be allowable at least because of their dependency on an allowable claim.

Additionally, claim 57 is further distinguished from the Zarling/Selvin combination because Zarling does not disclose a metallic coating. The Examiner proposes that Zarling refers to a “metal” coating because column 8, lines 9-23 refer to an up-converting phosphor associated with a dye that may “optionally be complexed with a heavy metal”, the dye being adsorbed to the inorganic up-converting phosphor crystal and/or covalently attached to a coated inorganic up-converting phosphor. The exact nature of the coating does not appear to be clear but the point is academic because clearly the disclosure is of a metal *complex*, i.e. not a metallic *coating*, as is now specified in claim 57, as amended.

Applicants also points out that new claims 74-79 reference lanthanides which are not specifically disclosed in Selvin. Thus, for example, claims 74-76 refer respectively to praseodymium, thulium and erbium as dopants, and these are not mentioned in Selvin. Similar considerations apply to claims 77-79.

In summary, the Examiner is respectfully requested to reconsider the pending claims in light of the above remarks, and to issue a Notice of Allowance for them. The undersigned attorney would welcome a telephone call from the Examiner if it is determined that further information or action is needed to place this application in better form for allowance.

Respectfully submitted

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